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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,432	11/10/2003	Wojtek Aucrbach	REG 784	4884

26693 7590 03/02/2006

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,432	AUERBACH ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed 12/02/2005 have been entered.

2. Claims 1-8 and 10-14 are cancelled.

3. Claim 9 is amended.

4. Claims 17-24 are newly added.

5. Rejection of claims 1-16 under 35 USC 112, first paragraph is withdrawn.

6. Claims 9, and 15-24 are examined in the instant application.

Claim Objections

Claim 9 is objected to for the following grammatical error. The word "a" should be inserted in line 1 before the word "mouse".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 17-20 are drawn to an in vitro method of directing a targeting vector to a specific chromosomal location within a genome of a mouse embryonic stem cell, comprising introducing into the cell a targeting vector, wherein the targeting vector comprises a drug resistance gene under control of a ubiquitin promoter.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses targeting any specific chromosomal location within a genome using the ubiquitin promoter.

Whereas the nature of the invention is a method of targeting a specific genetic sequence with a targeting vector, the art teaches that such a method would be unpredictable. The art

teaches that the ubiquitin promoter is ubiquitous existing throughout all eukaryotic cells (Tsirigotis et al. pg. 120, cols. 2-3 bridge pg. 121 col. 1).

The working examples provided by the specification teach that a targeting vector comprising a ubiquitin promoter was tested in ES cell colonies (pg. 10, Example 1). The specification continues to teach that particular genes were targeted, and that these genes were named T, D, F, N, P, 1R7, 20, L, E, and S respectively. The targeting vector comprises either the PGK or ubiquitin promoter to compare targeting efficiency. However, the specification has failed teach how one of skill in the art can target a specific chromosomal location with the claimed method of using a targeting vector comprising a ubiquitin promoter. As discussed above the ubiquitin promoter is ubiquitous, and would express in all eukaryotic cells. The specification teaches that certain genes were targeted, but the specification fails to teach that a specific chromosomal location was targeted. The working examples in the instant specification as well as the entire specification fail to teach how one of skill in the art would target a specific chromosomal location using the claimed method. Thus at the time of filing one of skill in the art would require an undo amount of experimentation without a predictable degree of success to make and use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, and 15-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rohozinski et al. (Genesis, 2002, Vol. 32, pgs. 1-7) in view of Tsirigotis et al. (BioTechniques, 2001, Vol. 31, pgs. 120-130) and Ghazizadeh et al. (J. Invest. Dermat., 1998 Vol. 111, pgs. 492-496) in view of applicants amendments filed 12/02/2005.

Claims 9 and 15-24 are drawn to an *in vitro* method of targeting a targeting vector into mouse embryonic stem (ES) cell, comprising introducing into said ES cells a targeting vector comprising a ubiquitin promoter, wherein the targeting vector comprises a drug resistance gene encoding neomycin phosphotransferase, hygromycin phosphotransferase, or puromycin acetyl transferase under control of a ubiquitin promoter, wherein said promoter is the ubiquitin C promoter that is a human, mouse, rat, or bacterial ubiquitin C promoter.

Rohozinski et al. teach a method of gene targeting in mouse ES cells via homologous recombination (pg. 1, Abstract). Rohozinski continues to teach that manipulating Y chromosome genes by homologous recombination in ES cells would be a direct way of addressing their function and testing the gene dosage hypothesis (pg. 1 col. 2 parag. 1 lines 1-4). Rohozinksi continues that successful targeting of the Y chromosome *Dby* and *Eif2s3y* genes using the disclosed method (pgs. 2-4). Rohozinksi does not teach the targeting of mouse ES cells with a targeting vector comprising the ubiquitin promoter.

Tsirigotis et al. teach that the ubiquitin promoter is one of the "best" promoters to achieve high levels of transgene expression in target cells (pg. 120 col. 3 last parag. bridge pg. 121 col. 1 lines 1-6). Tsirigotis continues to teach that transgenic mice were generated by microinjection of male pronuclei with an expression construct comprising the human ubiquitin C promoter and the GFP reporter gene as well as tested *in vitro* in HT4 murine neuroblastoma cells (pg. 121 col. 3 1st

full parag.). Tsirigotis et al. continues to teach that said transgenic mice and cells resulted in uniform expression of GFP due the ubiquitous expression of the ubiquitin promoter (pg. 122 col. 2-3 bridge pg. 123). Tsirigotis does not teach a targeting vector in mouse ES cells.

Ghazizadeh et al. teach using a retrovirus vector comprising the lacZ gene and the neomycin phosphotransferase gene the to select non-transformed porcine keratinocytes using the drug G418 to select cells which are not expressing neomycin phosphotransferase (pg. 493, col. 1 parag. 3). Ghazizadeh does not teach a method of targeting a targeting vector into mouse ES cells.

Thus the ordinary artisan would have been motivated by the teachings of Rohozinski to modify the methods taught by Tsirigotis and Ghazizadeh to target specific chromosomal locations in mouse ES cell colonies exhibiting drug resistance by using any drug resistant gene as a selection agent. Motivation is provided by Rohozinski teaching that manipulating specific chromosomal genes is advantageous to study gene function. Further motivation is provided by Tsirigotis teaching that the ubiquitin promoter is one of the best promoters to use. Further motivation is provided by Ghazizadeh teaching that drug resistance genes are used to select cells that express the transgene of interest. Thus the cited art provides the requisite teachings and motivation to make and us the claimed invention.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David A. Montanari, PhD

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER